Re-evaluation of the phenotype caused by the common *MATR3* p.Ser85Cys mutation in a new family

INTRODUCTION

Late-onset autosomal dominant vocal cord and pharyngeal distal myopathy (VCPDM) was first described in an American family.[1] A p.Ser85Cys mutation in *MATR3* gene was later identified in this family, and also in one Bulgarian family and very recently, in seven families—six German and one Asian.[2–4] Muscle pathology of VCPDM was dominated by rimmed-vacuolar fibre degeneration.[1 2] This year, two other mutations in *MATR3*, p.Phe115Cys and p.Thr622Ala, have been reported to cause autosomal dominant amyotrophic lateral sclerosis (ALS).[5] The original American p.Ser85Cys mutated family was re-evaluated and the authors stated: "These clinical findings supported reclassification of this condition as slowly progressive ALS, and the presence of upper motor neuron signs in the form of brisk reflexes ruled out myopathy as the only cause of disease in this family."[5]

We report a new family with the p.Ser85Cys mutation in *MATR3*, in which muscle atrophy and weakness are caused by progressive degenerative myopathy without any evidence of lower motor neuron defects.

METHODS

We investigated an American family with four affected siblings. Patients II.1, II.2 and II.4 were more extensively examined and followed for 7, 9 and 8 years, respectively. The father and one of his brothers were affected (figure 1A). Muscle MRI was performed in the proband (II.2) and in the younger brother (II.4). Muscle biopsies were obtained from three patients and examined by standard histochemical and immunohistochemical stainings with antibodies for Matrin 3, TDP-43, p62, SMI-31 and myosin A4.74, slow (MHCs), neonatal (MHCn) and developmental (MHCd) isoforms. Immunofluorescence analysis was performed with conventional methods using antibodies for G3BP and TIA1 C-terminus. Matrin 3 distribution was analysed from soluble cytoplasmic and nuclear fractions using western blotting.

Blood samples of all siblings in generation II were obtained and DNA was extracted by standard methods. Whole exome sequencing was performed on patient II.2 at ATLAS Biolabs GmbH using SeqCap EZ Human Exome Library V.2.0 (Roche NimbleGen), and captured DNA was sequenced on Illumina HiSeq 2000 platform, 2×100 bp. Reads were processed following the Genome Analysis Toolkit best practices pipeline and the Human Gene Mutation Database was used to detect previously reported pathogenic mutations. Sanger sequencing was performed to confirm the findings.

RESULTS

The age of onset ranged from 31 to 48 years, and the first manifestation was either weakness in the hands or legs causing difficulty in dexterity, or standing on heels and toes. The weakness slowly progressed to proximal upper and lower limb muscles. Wasting of the small hand muscles was evident followed by atrophy in the distal lower leg and forearm (figure 1B). Waddling and steppage gait was observed. Fasciculations were absent in all siblings. In two patients, brisk reflexes without clonus or spread were noted; there were no definite pathological pyramidal tract reflexes (Hoffman, crossed adductors, Babinski sign). Several years after disease onset, two patients had mild to moderate hypophonia and dysphagia. Two patients did not have respiratory symptoms; the other two had dyspnoea on exertion, reduced forced vital capacity (50%), or both.

Creatine kinase (CK) levels were normal or marginally elevated. Electromyography studies of all patients were consistent with myopathic changes. Fasciculations were absent. No chronic neurogenic changes (eg, large amplitude or long duration motor unit potentials) were observed in any of the studies. MRI showed marked fatty degeneration of dystrophic type in soleus and medial gastrocnemius in both patients studied (figure 1C). Less severe changes were observed in the anterolateral lower leg compartment and hamstrings in II.4. In muscle biopsy taken from the left tibialis anterior (II.2), there were numerous rimmed-vacuolated fibres (figure 1D). MyHC double staining showed a normal fibre type distribution without grouping. MHCd labelled most of the highly atrophic fibres and these were reactive for MHCn, although with less intensity in the moderately atrophic fibres and not in MHCd negative fibres. Matrin 3 immunohistochemistry showed a loss of protein in the central parts of myonuclei (figure 1D). Myofibrillar myopathy markers myotilin, desmin, αB-crystallin, and ectopic cytoplasmic dystrophin were negative, whereas TDP-43, p62, and SMI-31 accumulated in rimmed-vacuolar fibres (data not shown). Electron microscopy showed highly convoluted myonuclei. In immunofluorescent analysis, the TDP-43 binding partner TIA1 and TIA1 ligand G3BP showed increased expression. Matrin 3 analysed by western blotting showed no abnormalities compared to control (not shown).

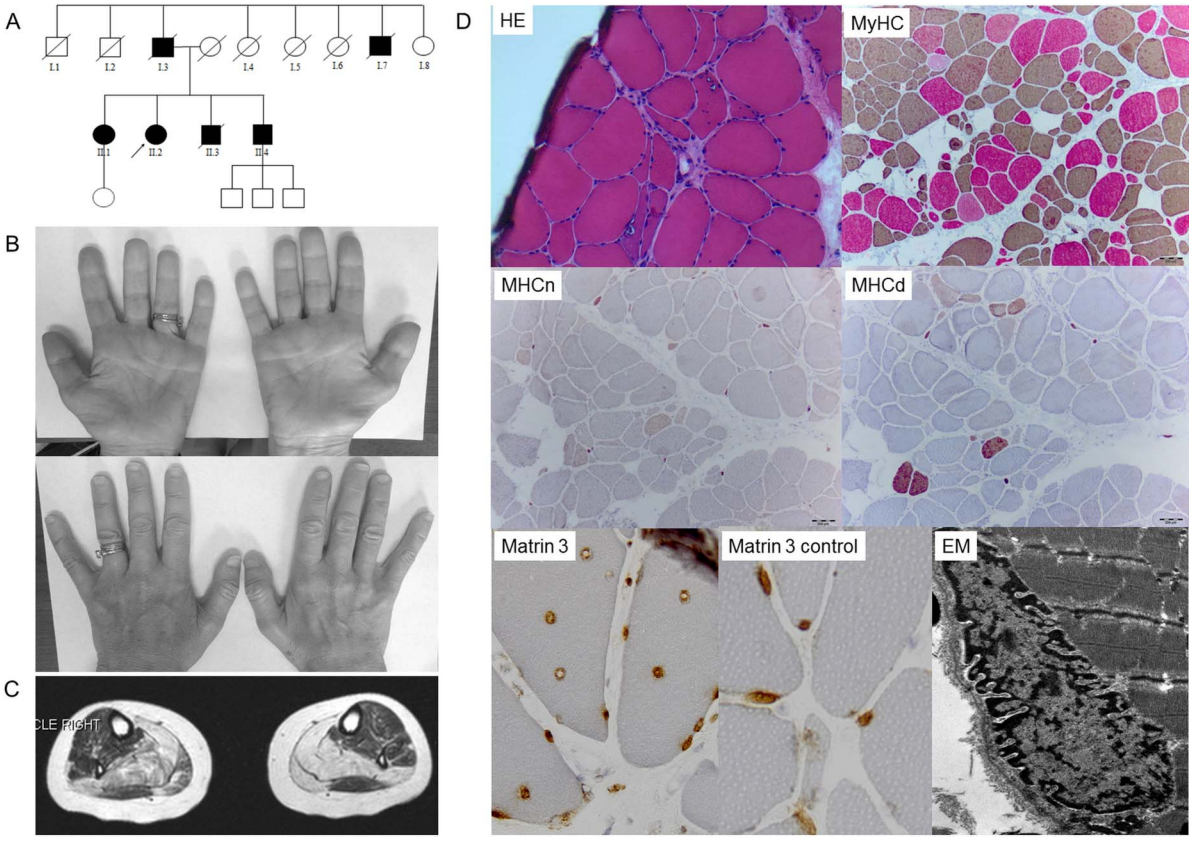

Figure 1 Pedigree and muscle findings of the family. Pedigree of the family (A). Wasting of the first dorsal interossei and thenar muscle of patient II.2 is seen on the right side (B). T1-weighted axial MRI scans of the lower legs of patient II.2 show prominent fatty degenerative changes in the soleus and medial gastrocnemius selectively sparing the lateral gastrocnemius and without significant changes in the anterior compartment (C). H&E stain section shows fibres with rimmed-vacuolar changes. Myosin heavy chain (MyHC) double staining with normal fibre type distribution, variation in fibre size ranging from highly atrophic rounded fibres to hypertrophic fibres, and numerous mostly rounded atrophic fibres of both type 1 (brown) and type IIa (red). Myosin heavy chain neonatal (MHCn) and developmental (MHCd) antibody reactivity in highly atrophic fibres and in moderately atrophic fibres. In internalised nuclei the central part showed depletion of Matrin 3 immunostaining with strong irregular label in the nuclear membrane. Matrin 3 normal control muscle showed a uniform reactivity in all myonuclei. Electron micrograph (EM) of the abnormally convoluted nuclear membrane.

Exome sequencing revealed a known mutation in *MATR3*: c.254C>G, p.Ser85Cys (NM_199189.2).[2] The mutation was Sanger sequenced and was present in all four of the affected siblings.

DISCUSSION

We report a new VCPDM family with the p.Ser85Cys mutation in *MATR3* showing less bulbar involvement, but respiratory failure in some cases. MATR3 as a cause of ALS was initially reported by Johnson *et al*[5] based on the identification of segregating mutations in several families and subsequently replicated in exome data derived from an independent cohort of patients diagnosed with familial ALS.[6] The pattern of combined features of ALS and myopathy has been recognised with other ALS-causing genes such as *CHCHD10*, *VCP*, *hnRNPA1* and *hnRNPA2B1*.[7–11] An assessment for a potential motor neuron component in our family showed brisk reflexes raising the possibility of minor upper motor neuron pathology, but there were no lower motor neuron abnormalities to account for the muscle atrophy.

Late-onset distal weakness with vocal cord and pharyngeal involvement has been the clinical hallmark of VCPDM.[1 2] However, bulbar symptoms can be absent in the beginning, as observed in our patients, and in a report of 16 German patients.[3] Respiratory insufficiency was evident in half of our siblings. The phenotype with this mutation is variable and the known hallmarks of the disease, dysphagia and dysphonia, can be subtle or absent. The distinct wasting of the first dorsal interossei and thenar muscles, with relative sparing of the hypothenar, was present in our patients, but never associated with clinical or electrophysiological fasciculations in muscles of the hands or elsewhere. Furthermore, motor unit potentials (MUPs) did not show increased duration or amplitude indicative of a chronic neurogenic process, but were clearly decreased in size indicating a myopathic process. Similarly, no changes compatible with a neurogenic process were observed on muscle biopsy. More than 10% of fibres expressed MHCd, in contrast to neurogenic atrophy where MHCn reactive atrophic fibres are far more frequent than MHCd reactive fibres. We, thus, conclude that with the *MATR3* p.Ser85Cys mutation in our family, the major process causing muscle atrophy and functional limitations is myopathic loss of muscle tissue.

Matrin 3 is a component of the nuclear matrix and has been associated with splicing and DNA replication.[12] The abnormal nuclear distribution of Matrin 3 in immunohistochemistry with normal result in western blotting suggests that the disease pathomechanisms do not involve quantitative changes in Matrin 3 expression, but rather mislocalisation of the protein. Matrin 3 interacts with TDP-43, a protein linked to ALS/frontotemporal dementia. TDP-43 and other autophagic markers, p62 and SMI-31, were components of the rimmed-vacuolar pathology in our patients. Increase of TIA1 reactive cytoplasmic granules and increased G3BP labelling suggest they are involved. G3BP is a key component of stress granules and a ligand of Matrin 3, which may contribute to the phenotype similarity with Welander distal myopathy.

The cases reported here show that distinguishing between myogenic and neurogenic pathomechanisms requires careful assessment of clinical, electrophysiological, muscle morphological and muscle MRI techniques.

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Notes